II. REMARKS

A. Status of the Claims

Claims 1, 3, 5, 7, 8, 10-16, 18-20, 36-41, 43-44, 52-54, and 56 are pending. Claim 1 has been amended without prejudice by the present amendment. Claims 17, 42, and 55 have been cancelled by the present amendment. Claims 2, 4, 6, 21-35, and 45-51 were previously cancelled.

B. Previous Rejections under 35 U.S.C. § 112

Applicants acknowledge with appreciation the Examiner's withdrawal of the rejections under 35 U.S.C. §112, first paragraph as indicated in the Advisory Action.

C. Rejections under 35 U.S.C. § 103

1. Kreek in view of the Dr. Medzon reference

In the Final Office Action, claims 1, 3, 5, 8, 12-14, 16-20, 44-47, 49-52 and 54-56 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek US 4,769,372 (hereinafter "the Kreek reference"), in view of Dr. Medzon (Clinical Toxicology Review) (hereinafter "Dr. Medzon"). This rejection was maintained in the Advisory Action.

In the Final Office Action, the Examiner stated the following:

> Kreek teaches an oral composition comprising combination of opioid analgesic and opioid antagonist (abstract, and column 5, lines 38-46). . . . The weight ratio of opioid antagonist of opioid analgesic is at least 0.01:1, which would fall within the claimed ranges (calculated from 1 mg of opioid antagonist and 100 mg of opioid analgesic).

Final Office Action of March 29, 2005 at pages 3-4.

The Examiner did state that Kreek does not teach naltrexone as an opioid antagonist. See Final Office Action at page 4. However, the Examiner also stated the following:

> Dr. Medzon teaches the use of naltrexone and nalmefene in place of naloxone for opioid detoxification. Naltrexone is used in an amount of 50-100 mg daily. Thus, it would have been obvious for one of ordinary skill in the art to modify the oral composition of Kreek using naltrexone as a suitable opioid antagonist, because Dr. Medzon teaches naltrexone by virtue of its' structural similarities to naloxone, shares the same properties exhibits by naloxone, because Dr. Medzon teaches naltrexone exhibits longer active opioid antagonists, and because Dr. Medzon teaches naltrexone has a high range of safety. The expected result would be a dosage form comprising combination of opioid agonists and naltrexone suitable for oral administ[ration] that exhibits a low level of toxicity, low incidence of undesirable side effects, and low incidence of opioid abuse.

Final Office Action at page 4 (citations omitted).

In the Advisory Action, the Examiner responded to the Applicants arguments in the response to Final Office action dated March 29, 2005, as follows:

> In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, Medzon is relied upon solely for the teaching of the equivalency of naltrexone and naloxone.

Advisory Action of August 3, 2005 at pages 2-3 (citations omitted).

This rejection is traversed. U.S. Patent No. 4,769,372 to Kreek (hereinafter "the Kreek reference") relates to a method of treating patients in chronic pain or suffering from chronic cough over a prolonged period to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility. The method includes the oral administration to the patient of dosage units comprising in combination opioid analgesics or antitussives and selected opioid antagonists which are substantially devoid of systemic antagonist activity when administered orally. (See, e.g., Abstract, and Col. 2, line 59 to Col. 3, line 3)

Dr. Medzon relates to the use of naltrexone and the use of nalmefene for the treatment of certain conditions such as, for example, opioid detoxification.

In the presently claimed invention, applicants claim an oral dosage form including a combination of an opioid agonist and naltrexone or a pharmaceutically acceptable salt thereof; wherein the combination is orally therapeutically effective for the treatment of pain and is selected from the specific opioid agonists in combination with naltrexone or a pharmaceutically acceptable salt thereof in certain ratios.

It is respectfully submitted that the Examiner's reliance on Dr. Medzon solely for the teaching of the equivalency of naltrexone and naloxone is incorrect as naltrexone and naloxone are not equivalents. According to Dr. Medzon (first paragraph) "[t]he success of naloxone in reversing opioid overdoses led to the search for longer acting opioid antagonists," and "naltrexone and nalmefene are two longer acting opioid antagonists that possess no opioid agonist activity." Therefore, in view of Dr. Medzon, one of ordinary skill in the art would understand that naltrexone is longer acting than naloxone. Further, it cannot be said that naloxone and naltrexone are equivalent as the commercially available product for naltrexone hydrochloride, Revia® (attached herewith as exhibit A), has an estimated oral bioavailability which ranges from 5% to 40%, whereas the Kreek reference itself states that the opioid antagonist for use therein (which includes naloxone) has little or no systemic bioavailability when taken by the oral route.

It is respectfully submitted that the Kreek reference teaches away from the use of naltrexone. The Kreek reference utilizes opioid antagonists which are "substantially devoid of systemic antagonist activity when administered orally." (See Kreek abstract). In contrast, as noted above, naltrexone has systemic bioavailability and antagonist activity when administered orally. The Kreek reference states that ". . . in order to be of practical use, any such antagonists to be orally administered as adjuncts to analgesic or antitussive agents must not substantially interfere with the analgesic or antitussive effects

of the opioid agonists administered to relieve pain or reduce cough (See col. 1, lines 53-58). Therefore, the Kreek reference teaches away from replacing the naloxone of the Kreek reference which is substantially devoid of systemic oral antagonist activity, with the naltrexone described in Dr. Medzon that "is available only in the oral form," and that when administered orally "competes with the opioid agonists for the mu, delta, and kappa receptor sites in the central nervous system." See Dr. Medzon at page 1 (*emphasis added*).

Further, ". . . [a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." See MPEP 8th Ed., 2nd Rev. § 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983). When viewed in its entirety, one skilled in the art would recognize that the Kreek reference, by specifically stating that the opioid antagonists used are substantially devoid of systemic antagonist activity when administered orally, teaches away from the use of an orally bioavailable opioid antagonist (e.g., naltrexone).

The Examiner is relying on Dr. Medzon for allegedly teaching "the use of naltrexone ... in place of naloxone". However, Dr. Medzon is directed toward the use of opioid antagonists to provide a systemic effect (e.g., such as opioid detoxification) and does not teach or suggest that naltrexone can be used in place of orally administrable naloxone when the intent is to utilize an opioid antagonist substantially devoid of systemic antagonist activity (as utilized in the Kreek reference). Further, as Dr. Medzon describes that naltrexone is used for opioid detoxification, it is respectfully submitted that one of ordinary skill in the art would not be motivated to administer an opioid in combination with naltrexone as recited in the present claims, as the administration of naltrexone in accordance with Dr. Medzon would compete for the mu, delta, and kappa receptor sites in the central nervous system with the opioid agonist being coadministered.

Even assuming arguendo that naltrexone was equivalent to naloxone (which it is not) and could simply be substituted for naloxone, it is respectfully submitted that the ratios exemplified in Table 2 of the Kreek reference are different that the ratios recited in the present claims. The following lists the ratios of the present claims and the ratios set

forth from Table 2 of the Kreek reference which are said to be typical unit and daily dosage for agonists and antagonists are as follows:

1. naltrexone : hydrocodone recited in claim 1: about 0.03:1 to about 0.27:1; the Kreek reference does not list a naloxone : hydrocodone ratio.

2. naltrexone : oxycodone recited in claim 1: about 0.037:1 to about 0.296:1; the Kreek reference describes a naloxone : oxycodone ratio of 0.6:1.

3. naltrexone : codeine recited in claim 1: about 0.005:1 to about 0.044:1; the Kreek reference describes a naloxone : codeine ratio of 0.2:1.

4. naltrexone : hydromorphone recited in claim 1: about 0.148:1 to about 1.185:1; the Kreek reference describes a naloxone : hydromorphone ratio of 1.2:1.

5. naltrexone : levorphanol recited in claim 1: about 0.278:1 to about 2.222:1; the Kreek reference does not list a naloxone : levorphanol ratio.

6. naltrexone : meperidine recited in claim 1: about 0.0037:1 to about 0.0296:1; the Kreek reference describes a naloxone : meperidine ratio of 0.04:1.

7. naltrexone : morphine recited in claim 1: about 0.018:1 to about 0.148:1 the Kreek reference describes a naloxone : morphine ratio of 0.2:1.

Therefore, if one would incorrectly assume that naloxone and naltrexone were equivalent, then the present claims would still not be taught or suggested by the combination of the Kreek reference with Dr. Medzon. However, it is respectfully submitted that this calculation of ratios does not even come into consideration, because as noted above, one of ordinary skill in the art would not substitute naltrexone for naloxone

as these are not equivalent and the Kreek reference teaches away from the use of an orally bioavailable opioid antagonist such as naltrexone.

Further, Applicants respectfully submit that the Kreek reference and the Medzon reference are improperly combinable. The Kreek reference is directed to opioid treatment for pain or cough, while the Medzon reference is directed to different disease states, including opioid detoxification. As Medzon is directed in part to opioid detoxification of patients, it is improperly combinable with the Kreek reference which is directed to the treatment of patients with opioids.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Kreek reference in view of Dr. Medzon be removed.

2. Kreek in view of the Dr. Medzon reference and Mitch et al.

Claims 7, 10, 11, 15, 48 and 53 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Kreek US 4,769,372, in view of Dr. Medzon (Clinical Toxicology Review) and Mitch et al. US 5,998,434 (hereinafter "the Mitch reference").

This rejection is traversed. The arguments above with respect to the rejection of claims 1, 3, 5, 8, 12-14, 16-20, 44, 52, and 54-56 are also applicable with respect to this rejection of dependent claims 7, 10, 11, 15 and 53. It is respectfully submitted that U.S. Patent No. 5,998,434 to Mitch et al. (hereinafter "the Mitch reference") fails in the very least to cure the deficiencies of the Examiner's rejection of the independent claims over the Kreek reference in view of Dr. Medzon.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Kreek reference in view of the Medzon reference and the Mitch reference be removed.

3. Kreek in view of the Dr. Medzon reference and the FDA consumer reference

Claims 10 and 36-43 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Kreek US 4,769,372, in view of Dr. Medzon (Clinical Toxicology Review) and FDA consumer."

This rejection is traversed. The arguments above with respect to the rejection of claims 1, 3, 5, 8, 12-14, 16-20, 44, 52, and 54-56 are also applicable with respect to this rejection of dependent claims 10 and 36-43. It is respectfully submitted that the FDA Consumer fails in the very least to cure the deficiencies of the Examiner's rejection of the independent claims over the Kreek reference in view of Dr. Medzon.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Kreek reference in view of the Medzon reference and the FDA consumer reference be removed.

III. CONCLUSION

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn.

An early and favorable action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned at the telephone number provided below if he believes that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J Paradiso
Reg. No. 41,240

DAVIDSON, DAVIDSON & KAPPEL, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940